REMARKS

Applicants appreciate the examination of the present application as evidenced by the Office Action dated October 9, 2009 (hereinafter, "the Office Action") issued responsive to Applicants' previously submitted Reasons for Pre-Appeal Brief Request for Review (hereinafter, "Pre-Appeal Brief") and Notice of Appeal both dated June 22, 2009. Upon entry of this Amendment, Claims 1, 3, 6-10, 12-16, 25, 28 and 31-39 are pending in the present application. Claims 1, 3, 6-10, 12-16, 25, 28 and 31-37 stand rejected.

In view of the foregoing amendments and following remarks to address the issues raised in the Office Action, reconsideration and withdrawal of the rejections to the present application are respectfully requested, and favorable action upon all pending claims is hereby requested. In the event that the present Amendment does not result in the indication of allowable subject matter, Applicants respectfully request the courtesy of an interview with the Examiner.

I. Claim Rejections Under 35 U.S.C. §112

Claims 1, 3, 6-10, 12-16, 25, 28 and 31-37 stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. *See* Office Action, page 2. More specifically, the Office Action asserts the following:

> [W]hile being enabling for the method for removal of abnormal infective prion proteins from an aqueous liquid consisting essentially of passing the liquid through a depth filter formed of a matrix comprising (a) a binder and (b) kieselguhr or perlite particles or mixtures thereof and having a pore size providing a retention less than 6 μm but more than the pore size that is too small for the plasma proteins to pass through . . . . [The specification] does not reasonably provide enablement for the claimed method wherein the pore size is in the range of 0.6 to 1.5 microns.

Office Action, pages 2 and 3.

In support of this assertion regarding the lack of enablement of the presently claimed invention, the Office Action further states the following:

> Applicants argue that Nebe's filter, which has a pore size of 2 μm, 0.8 μm and 0.2 μm would retain all soluble plasma proteins instead of passing the plasma proteins through the filter, which is the goal of the claimed method.... It is apparent that if the plasma proteins cannot pass through Nebe's filter... the plasma proteins cannot pass through the filter which has the pore size of 0.6 to 1.5 microns of the present invention. . . . Therefore contrary to Applicants statements, Applicant will not retain plasma proteins using the filter of pore size between 0.6 to 1.5 microns as required by claim 9.... Applicants have not shown that plasma proteins are able to pass through their filter of 6 or less microns. Applicants admit that plasma proteins cannot pass through the filter of 2.0 to 0.2 or 0.6 to 1.5 microns due to the size of plasma proteins. Applicants only speculate that plasma proteins will pass through the filter of 6 and less microns, which may or may not be true.... Example 1 does not show that albumin (70 kDa) passes through the filter.

Office Action, pages 4 through 7.

Applicants respectfully submit that principles of filtration technology have been mischaracterized and erroneously applied to aspects of the presently claimed invention as well as aspects of the cited references as discussed in greater detail in the remarks below.

Applicants admit that plasma proteins cannot pass through the filter of 2.0 to 0.2 or 0.6 to 1.5 microns due to the size of plasma proteins. Applicants only speculate that plasma proteins will pass through the filter of 6 and less microns, which may or may not be true.... **(Office Action, page 5)**

Applicants do not make such an admission. In fact, it should be noted that the desired plasma protein would pass through the filter recited in the pending claims, and as discussed below, Applicants note that plasma proteins will pass through a filter described in a cited reference– WO 96/05846 to Nebe (hereinafter, "Nebe"). Moreover, as evidenced by numerous literature references (see Table 1 attached herewith), it is well known that plasma proteins pass through filters with pore sizes at least as small as 0.2μm. As noted in Table 1, large protein molecules such as albumin, plasma protein fraction (a mixture of albumin and gamma globulin), immunoglobulin and von Willebrand Factor can pass through a 0.22 micron filter conclusively thereby demonstrating that smaller blood plasma protein molecules can pass through a filter having a pore size of 0.2 μm. Consequently, blood plasma proteins

in aqueous liquid can pass through a filter having a pore size "less than 6 μm" (claim 1), "in the range 0.6 to 6 microns" (claim 8) and "in the range 0.6 to 1.5 microns" (claim 9).

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Regarding the filters described in Nebe, Applicants respectfully submit that the Nebe **microfiltration pre-filters** are being confused with the subsequent **ultrafiltration** step. Applicants stated that the blood plasma proteins (and the prion proteins) pass through the Nebe pre-filters, however, both plasma proteins and prions are retained on the Nebe ultrafiltration membrane. Thus, filtration as utilized in the presently claimed invention does not occur in Nebe. To further illustrate, the Nebe process is summarized in Table 2 attached herewith. Table 2 also indicates the consequence of the proteins of interest cited in the present application when presented to each of the Nebe filters.

Filters having a pore size in the range of 0.2 μm to 6 μm are generally referred to as "microfiltration" filters and are typically used to remove solid debris from such plasma protein solutions. On the contrary, ultrafiltration membranes have pore sizes that are an order of magnitude smaller and are typically approximately 0.02 μm or less in effective pore size. Ultrafiltration membranes have a pore size that is commonly referred to in terms of the molecular weights of the molecule which pass through or are retained on the filters. Thus, an ultrafiltration membrane with a molecular weight cutoff of 30,000 kDa will retain molecules with such a molecular weight but will pass molecules with a smaller molecular weight. This property is illustrated in the attachment diagram entitled "Filtration Schematic." The schematic shows that a blood plasma protein will pass through a microfiltration filter of 6 μm, 2 μm, 0.8 μm and 0.2 μm. In contrast, blood plasma proteins will be retained on an ultrafiltration membrane of approximately 0.02 μm (equivalent to a molecular weight cutoff of approximately 30,000) as indicated in the previously submitted Pre-Appeal Brief. All plasma proteins of current interest have a molecular weight greater than 30,000 (expressed as 30 kDA) as follows– thrombin (36 kDa), coagulation factors and albumin (50-70 kDa), immunoglobulins (180 kDa) and von Willebrand factor (greater than 1,000 kDa). Abnormal

prion proteins generally have a size equal to or greater than 33 to 35 kDa and these would also be retained on an ultrafiltration membrane having a 30,000 molecular weight limit.

It is therefore clear that the blood plasma proteins in aqueous solution that are being filtered according to methods of the present invention will pass through microfiltration filters of pore size 6 μm, 2 μm, 0.8 μm and 0.2 μm yet be retained on ultrafiltration membranes whose effective pore size is typically an order of magnitude smaller, i.e., approximately 0.02 μm or less.

Example 1 does not show that albumin (70 kDa) passes through the filter. **(Office Action, page 6)**

Example 1 must be read in the context of the specification and in view of the knowledge of one skilled in the art where it is understood that blood plasma proteins pass through filters of pore size 0.22 μm as noted in Table 1. Clearly, such proteins would pass through the much wider K580 filters of Example 1 having a wider pore size of 0.6 to 1.5 μm.

At least based on the foregoing, Applicants respectfully submit that the specification is enabled under 35 U.S.C. §112, first paragraph, for the method for removal of abnormal infective prion proteins from an aqueous liquid consisting essentially of passing the liquid through a depth filter formed of a matrix comprising (a) a binder and (b) kieselguhr or perlite particles or mixtures thereof and having a pore size providing a retention less than 6 μm including methods wherein the pore size is in the range of 0.6 to 1.5 microns, and Applicants respectfully request that this rejection be withdrawn.

Additionally, in an effort to advance prosecution, Applicants have added new claim 38, which states that, in addition, the pore size is more than a pore size that is too small to allow passage of plasma proteins and the depth filter is a single use filter, and new claim 39 stating that the blood plasma product derived from plasma passes through the depth filter.

II. Claim Rejections Under 35 U.S.C. §103

Claims 1, 3, 6-10, 12-16, 25, 28 and 31-37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over GB 2 045 828 A to Ostreicher et al. (hereinafter, "Ostreicher et al.") in view of Nebe as evidenced by Encyclopedia Britannica. *See* Office Action, page 6.

The Office Action states, "Applicants arguments about the unexpected results (removing prions while letting plasma proteins pass through) is not supported in the specification. Additionally, the argued limitation: the plasma proteins pass through the filter is not recited in the claims. Applicants have not shown that plasma proteins are able to pass through their filter of 6 or less microns." Office Action, page 7. The Office Action further reiterates some of the points mentioned above in section I.

The Office Action concludes that "[s]ince Applicant uses the same filter size as the one disclosed in the prior art, the combination of Nebe's and Ostreicher's filters having the same pore size as the pore size claimed, will remove prions while letting plasma proteins pass through." Office Action, page 7 and 8.

Prior to the present invention, one of ordinary skill would have expected that prion proteins in aqueous solution would pass through a microfiltration filter of pore size 6 μm, 2 μm, 0.8 μm and 0.2 μm in the same way that normal blood plasma proteins pass through these same microfiltration filters. This hypothesis is exactly what results when the pre-filters employed by Nebe are used. The Nebe pre-filters of pore size 2 μm, 0.8 μm and 0.2 μm are employed to filter crude thymus extract solids, and as noted previously, the prion proteins do indeed appear to pass through these filters as evidenced by the poor reductions in infectivity reported by Nebe. Thus, the Nebe pre-filters are **ineffective** in completely removing prion protein infectivity, particularly given the contrasting Nebe evidence that the nylon pre-filters, which are of similar microfiltration pore size, do not retain prion proteins on the filter.

As discussed above, the unexpected results of removing prions and allowing plasma proteins to pass through are indeed supported in the specification and understood by those of ordinary skill in the art in view of the literature regarding filtration properties as noted above and supported by material attached herewith. Moreover, the fact that the plasma proteins are able to pass through the filters of 6 or less microns is implicit in the claim recitation where it

is clear that the plasma proteins of interest pass through the filters having the recited pore sizes. However, in an effort to advance prosecution and as noted above, Applicants have added new claim 38, which includes the recitation indicating that "the pore size is also more than a pore size that is too small to allow passage of plasma proteins," and new claim 39 reciting that "the blood plasma product derived from plasma passes through the depth filter."

Turning to the cited references, as discussed in the Pre-Appeal Brief, the combination of Nebe and Ostreicher would result in a non-functional filter. The filtration protocol described by Nebe involves three nylon pre-filters of pore size 2 μm, 0.8 μm and 0.2 μm ("microfiltration") followed by an ultrafiltration membrane which is an Amicon S1Y30 membrane of molecular weight limit of approximately 30 kDa (approximately equivalent to a pore size of approximately 0.02 μm or less). As discussed above, filtering an aqueous solution containing blood plasma proteins of interest together with prion protein contaminants would result in **both** the prion protein and the blood plasma protein of interest being captured on the ultrafiltration membrane. This consequence would not result in a process according to the present invention, since not only would the prion protein be removed, but the blood plasma protein of interest would also be removed on the ultrafiltration membrane. In contrast, the present invention is directed to removing the prion protein, surprisingly by microfiltration, yet allowing the aqueous solution containing the blood plasma protein of interest to pass through the filter. Only in this manner is the prion protein removed from the aqueous solution of blood plasma protein of interest according to embodiments of the present invention.

The combination of Nebe and Ostreicher results in non-functional filtration which teaches away from the present invention in that both prion proteins and blood plasma proteins of interest are removed following a process resulting from the combination of Nebe and Ostreicher. Accordingly, Applicants respectfully submit that the pending claims are not obvious under 35 U.S.C. §103(a) in view of the cited references, and Applicants respectfully request that this rejection be withdrawn.

III. Summary

Embodiments of the present invention are directed to the removal of prion proteins from an aqueous liquid containing natural products. The liquid containing the ***blood plasma protein will pass through the filter***, while the ***undesirable prion protein will be retained on the filter***. The cited references provide a product in which the blood plasma protein and the prion protein are not separated, i.e., the aqueous liquid provided by the combination of references ***does not*** include blood plasma proteins in which the prion proteins have been removed so that the aqueous liquid is non-infective with respect to prion protein infectivity.

CONCLUSION

Accordingly, Applicants submit that the present application is in condition for allowance and the same is earnestly solicited. The Examiner is encouraged to telephone the undersigned at 919-854-1400 for resolution of any outstanding issues.

Respectfully submitted,

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Attachments: Table 1, Table 2 and Filtration Schematic

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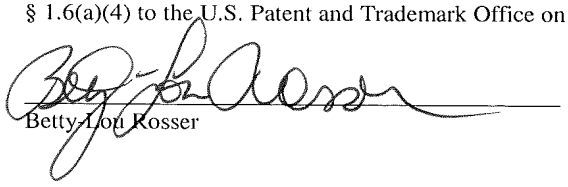

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Table 1. Filtration references

Reference	Specifics	Conclusion
United States Pharmacopia <1211>	Sterilization by filtration with pore sizes 0.22µm or 0.2µm.	Products will pass through the filter and bacteria will be retained by 0.22µm filter or smaller.
European Pharmacopoeia 5.1.1	Sterilization by filtration using a bacteria-retentive membrane with nominal pore sizes 0.22µm or less.	
United States Code of Federal Regulations 640.91	Plasma Protein Fraction undergoes final sterile filtration. Processing does not affect the product.	Plasma Protein Fraction (albumin and globulin) passes through a 0.22µm filter, without protein damage.
Martindale 29, 1248 d	Plasma Protein Fraction is sterilised by filtration.	
United States Code of Federal Regulations 640.81	Albumin undergoes final sterile filtration. Processing does not affect the product.	Albumin passes through a 0.22µm filter, without protein damage.
European Pharmacopoeia <0255>	Human albumin solution is passed through a bacteria-retentive filter.	
Martindale 29, 1215 j	Albumin is sterilised by filtration.	
European Pharmacopoeia <0338>, <0918>	Human normal immunoglobulin is passed through a bacteria-retentive filter.	Immunoglobulin passes through a 0.22µm filter, without protein damage.
Martindale 29, 1232 z	Normal immunoglobulin is sterilised by filtration.	
European Pharmacopoeia <0878>	Human antithrombin III concentrate is passed through a bacteria-retentive filter.	Antithrombin III passes through a 0.22µm filter, without protein damage.
European Pharmacopoeia <1224>	Human coagulation factor VII is passed through a bacteria-retentive filter.	Factor VII passes through a 0.22µm filter, without protein damage.
European Pharmacopoeia <0275>	Human coagulation factor VIII is passed through a bacteria-retentive filter.	Factor VIII passes through a 0.22µm filter, without protein damage.
European Pharmacopoeia <0223>	Human coagulation factor IX is passed through a bacteria-retentive filter.	Factor IX passes through a 0.22µm filter, without protein damage.
European Pharmacopoeia <0554>	Human prothrombin complex is passed through a bacteria-retentive filter.	Prothrombin complex (factors II, VII, IX and X) passes through a 0.22µm filter, without protein damage.
European Pharmacopoeia <2298>	Human von Willebrand factor is passed through a bacteria-retentive filter.	Von Willebrand factor passes through a 0.22µm filter, without protein damage.

Table 2. Nebe process

Filter series	Filter type	Filter size	Nebe outcome	Effect on the proteins (>30,000 molecular weight) of our invention
1	Pall nylon microfilter membrane	2.0 µm	Clarifies crude thymus extract	Pass through filter; not retained
2	Pall nylon microfilter membrane	0.8 µm	Clarifies crude thymus extract	Pass through filter; not retained
3	Pall nylon microfilter membrane	0.2 µm	Clarifies crude thymus extract	Pass through filter; not retained
4	Amicon S1Y30 ultrafilter – first time	30,000 molecular weight cut-off	Reduces scrapie infectivity, but still detectable	Retained by filter
4	Amicon S1Y30 ultrafilter – second time	30,000 molecular weight cut-off	No detectable scrapie infectivity	Retained by filter

Filtration Schematic